CHAPTER 20

Travel-Acquired Illnesses Associated with Fever

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The evaluation of fever in travelers poses a diagnostic challenge to clinicians for many reasons. First, there are many possible etiologies, some of which are geographically localized and are, thus, unfamiliar (**Table 20.1**). Diagnosis may be delayed owing to lack of familiarity with routes of infection or clinical presentations of these geographically limited illnesses. Fever in travelers may be caused by infections that are potentially fatal if not recognized and treated expediently, the most common of which is malaria (**Table 20.2**). Furthermore, some infectious diseases that cause fever in travelers are highly communicable (**Table 20.3**). These infections represent a considerable public health danger, and some have been associated with fatal nosocomial transmission. However, most febrile illnesses in travelers are self-limited and remain unconfirmed microbiologically, such as viral upper respiratory infections and gastrointestinal infections. Thus the challenge facing the clinician in the evaluation of fever in travelers is the detection of serious treatable or communicable infections while not submitting the majority of travelers with benign, self-limited causes of fever to expensive or invasive diagnostic evaluations. To succeed, the clinician must know as much as possible about the epidemiology, distribution, mode of transmission, and clinical characteristics of the etiologies of fever in travelers.

EPIDEMIOLOGY

Studies of fever in travelers have been impaired by the highly mobile nature of travelers and by the fact that travelers seek help abroad or fail to present to physicians at all. Large, prospective surveillance databases such as the GeoSentinel surveillance network and TropNet provide aggregate multinational data on ill travelers returning from destinations around the globe who present for care at designated "sentinel" clinics. In the GeoSentinel analysis by Wilson et al. (2007), 28% of ill returning travelers reported fever as their chief complaint. A lack of pre-travel counseling was associated with acquisition of a febrile illness abroad, as was visiting friends and/or relatives (VFR) travel. While there was no age bias in fever presentation, male travelers were more likely than female travelers to present with fever.

In retrospective, questionnaire-based studies, the incidence of "high fever over several days" in short-term (<3 weeks) travelers was 1.9%. Of the prolonged fevers reported, 39% occurred only while the traveler was abroad, 37% occurred both abroad and at home, and 24% occurred at home only. Prolonged fever was significantly associated with longer stays (>4 weeks) in the tropics. Among a large cohort of American short-term travelers to the developing world, undifferentiated fever occurred in 3%.

Most causes of febrile illnesses remain undiagnosed in retrospective surveys of travelers. However, in the GeoSentinel analysis by Wilson et al. (2007), malaria was the most common specific cause of fever in ill returned travelers, accounting for 21% of cases, while acute diarrheal disease and respiratory illness accounted for 15% and 14% of cases, respectively. Dengue, while less common, was still an important cause of fever, occurring in 6%

TABLE 20.1 Relative Risk of Travelers Contracting Infectious Diseases in Developing Countries

High Risk	Moderate Risk	Low Risk	Very Low Risk
Escherichia coli enteritis	Cryptosporidiosis	Amebiasis	Anisakiasis
Upper respiratory infection	Cyclosporiasis	Ascariasis	Anthrax
Viral gastroenteritis	Shigellosis	Chancroid	Chagas disease
Campylobacteriosis	Chikungunya	Cholera	
Chlamydia		Enterobiasis	Clonorchiasis
Dengue		Hepatitis B	Crimean-Congo hemorrhagic fever
Epstein-Barr virus		HIV	Diphtheria
Giardiasis		Leptospirosis	Ebola/Marburg hemorrhagic fever
Gonorrhea		Lyme disease	Echinococcosis
Hepatitis A		Malaria (with prophylaxis)	Filariasis
Herpes simplex		Rubella	Gnathostomiasis
Malaria (without prophylaxis)		Rubeola	Lassa fever
Salmonellosis		Schistosomiasis	Legionellosis
		Strongyloidiasis	Lymphogranuloma venereum
		Syphilis	Melioidosis
		Trichuriasis	Paragonimiasis
		Tropical sprue	Pinta
		Tuberculosis	Plague
	Typhoid fever		Polio
			Psittacosis
			Q fever
			Rabies
			Relapsing fever
		Rickettsial spotted fevers	
			Toxocariasis
			Trichinosis
			Trypanosomiasis
			Tularemia
			Typhus
			Yaws
			Yellow fever

HIV, Human immunodeficiency virus.

TABLE 20.2 Selected Potentially Fatal Febrile Tropical Infections with Established Treatments

Infection	Treatment
Viruses	
Crimean-Congo hemorrhagic fever	Ribavirin
Lassa fever	Ribavirin
Bacteria	
Anthrax	Penicillin
Bartonellosis	Penicillin, tetracycline, chloramphenicol, or streptomycin
Brazilian purpuric fever	Ampicillin or chloramphenicol
Brucellosis	Rifampin plus doxycycline; Tetracycline plus aminoglycoside or TMP/SMX
Leptospirosis	Penicillin or ampicillin, or doxycycline
Melioidosis	Ceftazidime
Plague	Streptomycin or tetracycline
Rickettsial spotted fevers	Doxycycline
Tuberculosis	Isoniazid, rifampin, ethambutol, plus pyrazinamide
Tularemia	Streptomycin or gentamicin
Typhoid fever	Ciprofloxacin, ceftriaxone, or azithromycin
Tick typhus	Doxycycline
Parasites	
Amebiasis (liver abscess)	Metronidazole followed by a luminal agent
African trypanosomiasis	Suramin or pentamidine; melarsoprol or difluoromethylornithine for central nervous system infection
Malaria	Atovaquone-proguanil; artemether-lumefantrine; artesunate or quinine or quinidine plus doxycycline
Schistosomiasis	Praziquantel (consider corticosteroids)
Visceral leishmaniasis	Sodium stibogluconate or liposomal amphotericin B

TMP/SMX, Trimethoprim/sulfamethoxazole.

TABLE 20.3 Selected Tropical Diseases with Documented Potential for Nosocomial Transmission

Argentine hemorrhagic fever (Junin)
Bolivian hemorrhagic fever (Machupo)
Crimean-Congo hemorrhagic fever
Ebola virus disease
Lassa fever
Marburg virus disease
Meningococcal infection
MERS-CoV
Plague
Rubella
Rubeola
SARS
Tuberculosis
Varicella

MERS-CoV, Middle East respiratory syndrome coronavirus; *SARS*, severe acute respiratory syndrome.

of returned ill travelers; with increasing numbers of outbreaks of dengue in regions popular with tourists over the past 5 years, such as the Caribbean, dengue is becoming increasingly recognized as a specific cause of fever in the returned traveler. Enteric fever and acute hepatitis, both vaccine preventable, were less common, diagnosed in only 2% and 1%, respectively, of febrile returning travelers. Rickettsioses were also rare as a cause of fever, occurring in only 2% of cases. Rates of hospitalization due to post-travel fever range from 20 to 30%, with *Plasmodium falciparum* malaria being the most likely specific cause of hospitalization in this setting.

In general, high-risk areas for the acquisition of febrile illnesses include sub-Saharan Africa, Southeast Asia, and Latin America. Sub-Saharan Africa and Oceania are "hot spots" for malaria acquisition, whereas South Central Asia contributes many cases of travel-acquired enteric fever (i.e., typhoid fever and paratyphoid fever due to *Salmonella enterica* serotypes Typhi and Paratyphi, respectively). Travelers returning with rickettsial infections have traveled almost exclusively to sub-Saharan Africa, while dengue infections are most commonly acquired in Southeast Asia, Latin America, and, increasingly, the Caribbean. With the emergence of chikungunya in the Americas in late 2013, and Zika in late 2015, these viral infections remain on the differential diagnosis of fever in travelers returning from all parts of the Caribbean, and Central and South America, as well as areas of prior endemicity, such as the Indian Ocean islands.

MEDICAL HISTORY

The medical history, including pre-travel preparation and the details of activities and exposures during travel, is essential in identifying the differential diagnosis of fever in travelers.

Vaccinations and Prophylaxis

First, always establish the patient's vaccination status. No vaccination is 100% effective; efficacy ranges from the near-perfect, 10-year protection provided by yellow fever vaccine to the approximately 65% efficacy of both the injectable and oral typhoid vaccines. The efficacy of the current hepatitis A and hepatitis B vaccine series is >90%. When a dose of oral polio vaccine is repeated in adult life, as recommended for risk of exposure, vaccine efficacy approaches 90-100%. Thus, a documented history of recent vaccination administered appropriately renders the diagnosis of yellow fever, hepatitis A, hepatitis B, or polio unlikely, while illnesses with poorer vaccine efficacy, such as typhoid fever and influenza, remain more probable. Similarly, administration of immune globulin within 3 months of exposure makes hepatitis A highly unlikely.

A history of compliance with prophylaxis for malaria or traveler's diarrhea is helpful, although one should bear in mind that prophylaxis for malaria is not 100% effective (see Chapters 6 and 21). It is also important to inquire as to previous diagnostic tests and treatment, some of which may have occurred while traveling.

Exposures

It is important to learn the details of itinerary, duration, and style of travel, as well as the particular characteristics of a given trip, to ascertain the risk of serious disease presenting as fever. The travel itinerary is important because many diseases are limited in their geographic distribution (see **Tables 20.6, 20.8, 20.10, 20.11, and 20.12**). In addition to geographic exposure, there may be a significant association between length of travel and serious illness, and infections vary significantly between short-term travelers and immigrants exposed to similar conditions in the same geographic area.

For example, schistosomiasis may present as Katayama fever (acute schistosomiasis) among travelers, but this syndrome is rarely observed in individuals born and raised in endemic areas, who may present as immigrants with symptoms of chronic schistosomiasis, such as abdominal discomfort, ascites, and splenomegaly (Chapter 48). Age at time of exposure, underlying health, genetic factors, and intensity and duration of parasite exposure probably contribute to these differences.

Travel style can be associated with an increased risk of serious illness, especially if an individual resided with locals or participated in an "adventure tour" as opposed to staying in urban, first-class hotels. Travel on cruise ships is a notorious risk factor for norovirus infection and invasive bacterial gastroenteritis. Younger age and being a student also increase the risk of becoming ill while traveling.

Exposures are clues that can narrow the differential diagnosis (**Table 20.4**). It is important to inquire specifically about arthropod bites, animal contact, sexual behavior, blood- and body-fluid exposures from injections or transfusions of blood products, caring for ill individuals (see **Table 20.3**), and ingestion of unpurified water, unpeeled raw fruits, raw vegetables, raw or undercooked meat/seafood, or unpasteurized dairy products. One should inquire about bathing or swimming in fresh water in areas where schistosomiasis or leptospirosis are prevalent. Barefoot exposure to sand or soil establishes risk for geohelminth infections such as strongyloidiasis and hookworm infection. Travelers may be reluctant to volunteer information regarding sexual contact abroad, but a complete sexual history is always warranted.

Patients such as volunteers, missionaries, long-term expatriates, and military personnel may present with diseases seen in both travelers and immigrants, presumably reflecting more intense and prolonged exposures.

Clinical Characteristics

Incubation Period

It is important to establish the onset of fever in relation to exposures, because the incubation period of illness can narrow the diagnostic possibilities. Some infections may present long after exposure, such as amebic liver abscess, malaria (especially if due to *Plasmodium vivax*, *P. ovale*, or *P. malariae*), human immunodeficiency virus (HIV), brucellosis, hepatitis B, tuberculosis, visceral leishmaniasis, and human African trypanosomiasis. It is also helpful to note whether the course of illness has been acute or chronic. **Table 20.5** is helpful as a guide, but many of the chronic illnesses listed, such as American and African trypanosomiasis, may also present as acute febrile syndromes during primary infection.

Interval to presentation can serve as a proxy for incubation period. *Falciparum* malaria is most likely to present in the 7- to 14-day post-travel window, whereas malaria due to *P. vivax* may present beyond 42 days post-travel. Dengue seldom presents beyond 10 days post-travel, and chikungunya and rickettsioses rarely beyond 12 days. Similarly, fever due to common agents of traveler's diarrhea or influenza rarely present beyond 1 week post-travel.

Fever Patterns

Fever patterns, although potentially helpful, may not be as characteristic of certain diseases in short-term travelers as they are in immigrants. Fevers of primary malaria rarely exhibit the intermittent pattern of tertian or quartan fevers (every 2 or 3 days, respectively) characteristically experienced by partially immune individuals. "Saddle-back fever," which refers to the phenomenon in which fever lysis is followed within several days by the resumption of high fevers, is found in 60% of cases of dengue fever but can also be seen in relapsing fever resulting from *Borrelia* species or with *P. malariae* (quartan malaria) infection, leptospirosis, and many arboviral infections other than dengue. Continuous fever with temperature/pulse dissociation (relative bradycardia) is often present in enteric (typhoid or paratyphoid) fever, tick typhus, and arboviral infections. Remittent fevers, in which the body temperature fluctuates more than 2°C (3.6°F) but does not completely return to normal, can occur in pulmonary tuberculosis but may also be seen with bacterial sepsis and bacterial abscesses.

Specific Symptoms

Specific symptoms may help establish a diagnosis. Severe myalgia and arthralgia, although characteristic of many febrile illnesses, are extremely severe in arboviral infections such as

TABLE 20.4 Exposures Suggesting Specific Infections

Animal contact
- Anthrax
- Babesiosis
- Brucellosis
- *Capnocytophaga canimorsus*
- Hantavirus
- Lassa fever
- Leptospirosis
- Plague
- Psittacosis
- Q fever
- Rabies
- Rat-bite fever
- Toxoplasmosis
- Viral hemorrhagic fevers
- All tick-borne diseases

Ticks, fleas, lice, mites
- Anaplasmosis
- Babesiosis
- Colorado tick fever
- Crimean-Congo hemorrhagic fever
- Ehrlichiosis
- Kyasanur Forest disease
- Lyme disease
- Murine typhus
- Omsk hemorrhagic fever
- Plague
- Q fever
- Relapsing fever
- Rickettsial spotted fevers
- Rickettsialpox
- Scrub typhus
- Tick-borne encephalitis
- Tularemia
- Typhus

Transfusions or injections
- Babesiosis
- Bartonellosis
- Chagas disease
- Hepatitis B and C
- HIV
- HTLV-1
- Leishmaniasis
- Malaria
- Q fever
- Toxoplasmosis

Raw/uncooked meat/seafood
- Cholera
- Hepatitis A
- Toxoplasmosis
- Trichinosis
- *Vibrio parahaemolyticus*, *Vibrio vulnificus*
- Viral gastroenteritis

TABLE 20.4 Exposures Suggesting Specific Infections—cont'd

Sexual contact
- Chancroid
- Chlamydia (PID)
- Gonorrhea (PID and disseminated infection)
- Granuloma inguinale
- Hepatitis B (and possibly C)
- Herpes simplex
- HIV
- HTLV-1
- Lymphogranuloma venereum
- Syphilis
- Trichomoniasis

Mosquitoes
- Bancroftian filariasis
- Alphavirus diseases
  - Chikungunya
  - Eastern equine encephalitis
  - Mayaro fever
  - O'nyong-nyong
  - Ross River
  - Sindbis
  - Venezuelan equine encephalitis
  - Western equine encephalitis
- Flavivirus diseases
  - Dengue
  - Japanese encephalitis
  - St. Louis encephalitis
  - Yellow fever
  - Zika virus
- Others
  - Bunyavirus diseases
  - La Crosse
  - Oropouche
  - Rift Valley fever
  - Tahyna

Fresh water (or unpeeled fruits/vegetables)
- Amebiasis
- *Campylobacter* enteritis
- Cryptosporidiosis
- Cyclosporiasis
- Hepatitis A and E
- Leptospirosis
- Salmonellosis (typhoid fever)
- Schistosomiasis
- Shigellosis
- Viral gastroenteritis

Ingestion of unpasteurized milk
- Brucellosis
- Listeriosis
- Q fever
- Salmonellosis
- Tuberculosis

HIV, Human immunodeficiency disease; *HTLV-1*, human T-cell lymphotropic virus type 1; *PID*, pelvic inflammatory disease.

TABLE 20.5 Selected Febrile Illnesses of Travelers Classified by Incubation Period and Typical Clinical Course

SHORT INCUBATION (<28 DAYS)		LONG INCUBATION (>28 DAYS)	
Acute Course	**Prolonged or Relapsing Course**	**Acute Course**	**Prolonged or Relapsing Course**
Arbovirus infection	Brucellosis	African trypanosomiasis	African trypanosomiasis
Bacterial dysentery	Epstein-Barr virus	Amebiasis	Amebiasis
Childhood viruses	Q fever	Hepatitis B and C	American trypanosomiasis
Chikungunya			
Dengue	Relapsing fever	Malaria	Brucellosis
Ebola virus disease			
Hepatitis A and E	Schistosomiasis	Rabies	Filariasis
Influenza	Typhoid fever		Leishmaniasis
Leptospirosis			Melioidosis
Malaria			Paragonimiasis
Plague			Schistosomiasis
Rickettsial spotted fevers			Strongyloidiasis
Rubella			Tuberculosis
Rubeola			
Tularemia			
Typhus			
Yellow fever			

Adapted in part from: Salata, R.A., Olds, R.G., 1990. Infectious diseases in travelers and immigrants. In: Warren, K.S., Mahmoud, A.A.F. (Eds.), Tropical and Geographic Medicine, second ed. McGraw-Hill, New York.

chikungunya and dengue. Chills are especially prominent in malaria, bacterial infections or sepsis, and dengue. Spontaneous bleeding suggests the possibility of infection with one of the hemorrhagic viruses (e.g., Lassa fever, yellow fever, dengue hemorrhagic fever) but is also reported with various bacterial and rickettsial diseases (**Table 20.6**). Bleeding may range from easy bruising typical of mild dengue to severe epistaxis, gastrointestinal bleeding, and possible spontaneous central nervous system hemorrhage seen with severe hemorrhagic viral diseases.

Diarrhea associated with fever is typically caused by common bacterial agents of traveler's diarrhea such as *Campylobacter* species, enterohemorrhagic, enteroaggregative, and enteroinvasive *Escherichia coli* strains, *Salmonella* species, *Shigella* species, *Entamoeba histolytica*, and intestinal viruses. Occasionally, febrile diarrhea may present due to other gastrointestinal pathogens such as hookworm, coccidia such as *Cyclospora cayetanensis* or *Cryptosporidium*, and rarely with *Giardia lamblia*. However, many systemic illnesses can present with diarrhea, including malaria.

Respiratory symptoms that suggest viral upper respiratory infections may be manifestations of tuberculosis, bacterial pneumonia, Q fever, melioidosis, or the pulmonary migration phase of helminths such as *Ascaris lumbricoides* and *Strongyloides stercoralis*. Fever with localized respiratory signs and symptoms in a traveler to South Central or Southeast Asia should raise the specter of highly pathogenic avian influenza or severe acute respiratory syndrome

TABLE 20.6 Important Tropical Infections Associated with Spontaneous Bleeding

Infection	Geographic Distribution
Viruses	
Argentine hemorrhagic fever (Junin)	South America
Bolivian hemorrhagic fever (Machupo)	South America
Chikungunya	The Americas (Caribbean, Central and South America), Africa, Asia, Indian subcontinent
Crimean-Congo hemorrhagic fever	Africa, Asia, and Eastern Europe
Dengue	Tropical regions of Africa, South America, Central America, the Caribbean, Asia, and Oceania
Ebola virus disease	Africa
Hantaan virus (hemorrhagic fever with renal syndrome)	Asia, Africa, Oceania, the Americas, Europe
Kyasanur Forest disease	India
Lassa fever	Africa
Marburg virus	Africa
Omsk hemorrhagic fever	Asia (the former USSR)
Rift Valley fever	Africa
Yellow fever	Africa and South and Central America
Bacteria	
Brazilian purpuric fever	South America
Leptospirosis	Widespread
Meningococcal infection	Widespread, particularly sub-Saharan Africa
Melioidosis	Asia, Oceania, Africa, and focal spots in the Americas
Plague	Asia, Africa, Europe, and the Americas
Rocky Mountain spotted fever	North and South America
Typhus	Widespread
Vibrio vulnificus	Widespread in coastal regions

Adapted in part from: Wilson, M.E., 1991. A World Guide to Infections: Diseases, Distribution, Diagnosis. Oxford University Press, New York.

(SARS). Middle East respiratory syndrome coronavirus should be considered when evaluating fever, respiratory symptoms, and recent travel to the Middle East or Korea.

Hepatosplenomegaly along with fever suggests malaria, mononucleosis, hepatic amebiasis, acute schistosomiasis (Katayama fever), visceral leishmaniasis, or enteric fever, among other infectious diseases. Lymphadenopathy evokes mononucleosis, HIV, acute schistosomiasis, plague, typhoid fever, tularemia, and trypanosomiasis, among others (**Table 20.7**). Of course, neoplastic and collagen vascular diseases may also induce lymphadenopathy and fever.

Meningismus, confusion, and other signs of central nervous system dysfunction may be caused by a variety of viral, parasitic, and bacterial agents (**Table 20.8**). Many of these pathogens are restricted to certain ecologic niches, so the patient's geographic itinerary, season of travel, and exposure history are essential. For example, Japanese encephalitis virus is limited to the Far East, is a disease of summer in temperate climates, and is transmitted by mosquitoes. Spinal cord disease associated with fever can result from West Nile virus, schistosomiasis, human T-cell lymphotrophic virus type 1 (HTLV-1) infection, or polio virus infection.

TABLE 20.7 Selected Febrile Illnesses Causing Organomegaly and/or Lymphadenopathy

	Hepatomegaly	Splenomegaly	Generalized Adenopathy	Localized Adenopathy
Viruses				
Cytomegalovirus	+/–	+	+/–	+/–
Dengue	+/–	+/–	+	–
Epstein-Barr virus	+/–	+ +	+ +	+
Hepatitis A and B	+ +	+/–	+/–	–
HIV	+/–	+/–	+ +	+
HTLV-1	+ +	+ +	+ +	+/–
Bacteria				
Anthrax	–	–	–	+
Brucellosis	+	+ +	+	+/–
Ehrlichiosis	+	+	–	–
Endocarditis	–	+	+/–	–
Enteric fever	+ +	+ +	+/–	–
Leptospirosis	+/–	+	+	–
Melioidosis	+/–	+/–	+	+
Plague	+	+	–	+ +
Q fever	+ +	+ +	–	–
Relapsing fever	+ +	+ +	+/–	+/–
Spotted fevers	+	+	+/–	+/–
Tuberculosis	+/–	+/–	+/–	+ +
Tularemia	+/–	+/–	+/–	+ +
Typhus	+/–	+ +	+/–	–
Parasites				
Acute schistosomiasis	+ +	+ +	+ +	+/–
African trypanosomiasis	+/–	+	+ +	+
Amebiasis (hepatic)	+ +	+/–	–	–
Babesiosis	+ +	+ +	+/–	+/–
Fascioliasis	+ +	+/–	–	–
Filariasis	–	–	+	+ +
Malaria	+ +	+	–	–
Toxocariasis visceral larva (migrans)	+ +	+/–	–	–
Toxoplasmosis	+/–	+/–	+	+
Visceral leishmaniasis	+ +	+ +	+	+ +

– No association; + Finding is associated; ++ Finding strongly associated; +/– Finding may or may not be present.
HIV, Human immunodeficiency virus; *HTLV-1*, human T-cell lymphotropic virus type 1.

TABLE 20.8 Important Tropical Infections Causing Meningitis and Encephalitis

Infection	Geographic Distribution
Viruses	
California group encephalitis	The Americas and Asia
Chikungunya	The Americas (Caribbean, Central and South America), Africa, and Asia
Crimean-Congo hemorrhagic fever	Africa, Asia, and Europe
Japanese encephalitis	Asia and Oceania
Kyasanur Forest disease	Asia (India)
Lymphocytic choriomeningitis	Widespread
Murray Valley encephalitis	Oceania (Australia)
Omsk hemorrhagic fever	Europe (former USSR)
Oropouche	South America
Poliomyelitis	Africa and Asia
Rabies	Africa, the Americas, Asia, and Europe
Rift Valley fever	Africa
Tick-borne encephalitis	Asia and Europe
Venezuelan equine encephalitis	The Americas
West Nile fever	Africa, Asia, Europe, and Oceania
Bacteria	
Bartonellosis	South America (Andes)
Brucellosis	Widespread
Leptospirosis	Widespread
Listeriosis	Widespread
Lyme disease	Widespread (especially America and Europe)
Meningococcal infection	Widespread (especially sub-Saharan Africa, northern India, and Nepal)
Rickettsioses	Widespread
Salmonellosis	Widespread
Syphilis	Widespread
Tuberculosis	Widespread
Fungi	
Blastomycosis	Africa, the Americas, Asia, and Europe
Coccidioidomycosis	The Americas
Cryptococcosis	Widespread
Histoplasmosis	Widespread
Paracoccidioidomycosis	Amazonas, Brazil
Sporotrichosis	Widespread
Protozoa	
African trypanosomiasis	Africa, primarily East Africa (game parks)
Malaria	Widespread
Primary amebic meningoencephalitis	Widespread
Toxoplasmosis	Widespread

Continued

TABLE 20.8 Important Tropical Infections Causing Meningitis and Encephalitis—cont'd

Infection	Geographic Distribution
Helminths	
Cysticercosis (*Taenia solium*)	Widespread
Eosinophilic meningitis (*Angiostrongylus cantonensis*)	Asia, Oceania, Africa, and the Americas
Gnathostomiasis	Asia, Oceania, Africa, and the Americas
Paragonimiasis	Africa, Asia, South America
Strongyloidiasis (in immunocompromised hosts)	Widespread
Toxocariasis	Widespread
Trichinosis	Widespread

Adapted in part from: Wilson, M.E., 1991. A World Guide to Infections: Diseases, Distribution, Diagnosis. Oxford University Press, New York.

Cutaneous manifestations of disease are common but seldom specific (**Table 20.9**). The erythema chronicum migrans of Lyme disease and rose spots in typhoid fever are examples of unique, specific rashes. Nonetheless, rash can refine a differential diagnosis considerably. For example, an eschar at the site of inoculation is typical of tick typhus, boutonneuse (Mediterranean spotted) fever, and anthrax. Cutaneous ulcers are seen in leishmaniasis, tropical phagedenic ulcer, Buruli ulcer (*Mycobacterium ulcerans*), cutaneous amebiasis, arthropod bites, syphilis, yaws, tuberculosis, and leprosy. When evaluating a patient who has received previous treatment, it is important to recall that rash and fever can be caused by reactions to drugs, such as sulfa drugs, antimalarials, and other antibiotics. Rickettsial diseases are frequently associated with rash, but the absence of rash may be misleading and does not exclude the possibility of rickettsial disease (see **Table 20.13**). Genital ulcers, such as those seen with syphilis, chancroid, and lymphogranuloma venereum, should be construed as markers of exposure to other sexually transmitted diseases that should be excluded in affected travelers, as well.

APPROACH TO THE TRAVELER WITH FEVER

A thorough but directed evaluation, bearing in mind that most fevers are self-limited, is warranted for the traveler presenting with fever. A careful history covering pre-travel prophylaxis, itinerary, travel style and exposures, apparent incubation period, fever pattern, symptoms, previous treatment, and diagnostic studies is essential. Laboratory tests to consider in the diagnostic evaluation include blood smears for malaria (and *Borrelia*, trypanosomes, *Babesia*, etc.), complete blood count and white cell differential, absolute eosinophil count, serum electrolytes, blood urea nitrogen and creatinine, glucose, bilirubin, hepatic transaminases, urinalysis, chest radiograph, tuberculin skin test, hepatitis serologies, and bacterial cultures of blood, urine, and stool. In many instances, it is prudent to obtain and save an acute serum sample for future comparative serologic studies. Suspected cases of viral hemorrhagic fevers, severe malaria, and enteric fever should be immediately hospitalized. Travel in a rural African environment is a significant risk factor for exposure to viral hemorrhagic fevers, although other hemorrhagic viruses, including those causing dengue fever, Hantaan, yellow fever, and Crimean-Congo hemorrhagic fever, have a more cosmopolitan distribution in widely scattered parts of the world (**Table 20.6**). All cases of suspected viral hemorrhagic fevers should be reported immediately to both the local health department and the Centers for Disease Control and Prevention (CDC).

The clinically stable patient with travel-related fever in whom the initial history, physical examination, and screening laboratory studies, including at least two blood films for malaria

TABLE 20.9 Selected Infections Characteristically Associated with Fever and Cutaneous Signs

Infection	Typical Skin Manifestations/Rash
Viruses	
Dengue	Diffuse scarlatiniform or macular rash; occasional petechiae or ecchymoses
Ebola/Marburg viruses	Maculopapular rash on trunk
Herpes simplex virus	Vesicles
HIV (acute)	Morbilliform rash
Rubella	Maculopapular rash
Rubeola	Maculopapular rash
Varicella	Vesicles or pustules
Viral hemorrhagic fevers	Petechiae, ecchymoses
Yellow fever, hepatitis viruses	Jaundice
Bacteria	
Anthrax	Eschar
Bartonellosis	Angioproliferative papules and nodules
Leptospirosis	Possible pretibial maculopapular rash
Lyme disease	Large, annular erythematous macule(s)
Meningococcal infection	Petechiae and purpura, may involve palms/soles
Rickettsial spotted fevers	Diffuse macular or maculopapular rash, may involve palms/soles; possible petechiae and eschar at primary inoculation site
Scarlet fever	Diffuse maculopapular rash
Scrub typhus	Eschar; diffuse macular or maculopapular rash
Syphilis (secondary)	Papular rash, possibly involving palms/soles
Tularemia	Ulcerated papule at inoculation site
Typhoid fever	Rose-colored papules on trunk ("rose spots")
Typhus	Diffuse macular or maculopapular rash; occasional petechiae
Parasites	
Acute schistosomiasis (Katayama fever)	Urticaria
African trypanosomiasis	Chancre, followed by generalized erythematous rash; possible erythema nodosum
American trypanosomiasis	Erythematous nodule at inoculation site; may be associated with periorbital edema
Leishmaniasis	Ulcers, nodules
Onchocerciasis	Subcutaneous nodule(s), dermatitis
Strongyloidiasis	Cutaneous larva currens (erythematous, serpiginous subcutaneous papules, often perirectal, associated with pruritus)

HIV, Human immunodeficiency virus.

separated by >6 but not more than 24 hours, are unremarkable may be observed. The patient should be instructed to keep a temperature record and return in 2-3 days if fever fails to resolve, or sooner if symptoms worsen. Empiric treatment for enteric fever (and/or rickettsioses) may be considered in patients who continue to have fever >48 hours after all diagnostic work-up has been initiated but in whom specific tests have been noncontributory

(see Public Health Agency of Canada, Fever in the Returning Traveller 2011). Because the majority of travel-related febrile illnesses are self-limited viral syndromes, most fevers will resolve spontaneously. If fever persists, however, repeat malarial smears and blood cultures are warranted. Directed serologic studies to detect diseases compatible with the patient's history and physical examination should be considered. Imaging studies (e.g., abdominal computed tomography or ultrasound) and biopsies (e.g., bone marrow, liver, lymph nodes) may be indicated. Hospitalization may be justified to expedite the work-up in certain circumstances. During the evaluation of perplexing cases of apparent travel-related illness, the clinician should bear in mind that non-infectious disorders, such as pulmonary embolism, occult malignancies, systemic lupus erythematosus, and temporal arteritis, may present with fever.

Presumptive empiric therapy directed against a likely pathogen may be justified, especially when adequate diagnostic studies are not readily available or a patient is clinically deteriorating. Examples include intravenous artesunate for suspected severe infection with *P. falciparum*, quinolones or third-generation cephalosporins for suspected enteric fever, doxycycline for suspected rickettsioses, and ribavirin for suspected Lassa fever (**Table 20.2**). Early initiation of appropriate therapy may significantly reduce morbidity and potential mortality from these serious febrile illnesses of travelers.

INFECTIOUS DISEASES IN THE TRAVELER WITH FEVER

Selected infectious diseases that should be considered in the traveler with fever are discussed in this section, with the goal of providing an overview. References to other chapters in this book are given as appropriate; however, the reader is encouraged to consult, when possible, standard textbooks on infectious diseases and tropical medicine and to contact the CDC for current and detailed information on the diagnosis and treatment of exotic diseases. The experts at the CDC can provide 24-hour emergency medical consultation by telephone to healthcare providers dealing with a very ill patient.

Malaria

Fever in a traveler from a malarious area should be evaluated carefully, with multiple blood smears for malaria. Although malaria is discussed in greater detail in Chapter 21, key points are worth repeating here. *P. falciparum* infection can be life-threatening when associated with high parasitemia, blackwater fever, cerebral malaria, or acute respiratory distress syndrome. Chemoprophylaxis is often effective, but only when taken as directed. Of the 231 cases of severe malaria in travelers reported to the CDC in 2012, 75% were due to *P. falciparum*, and 79% of these infections were acquired in sub-Saharan Africa; only 7 of 200 patients in whom information on prophylaxis was known were adherent to their drug regimen. However, drug-resistant *P. falciparum* is now widespread, and even perfect compliance with prophylaxis does not provide absolute protection from malaria infection. The case-fatality rate for *P. falciparum* in US travelers was approximately 0.4% in 2012 (6 deaths among 1687 total cases). Clinical manifestations of *P. vivax* and *P. ovale* infections can develop up to 5 years after exposure. The diagnosis of malaria in immune individuals or individuals who have received prophylaxis or partial treatment may be complicated by low parasitemia. Multiple blood smears in combination with highly sensitive rapid diagnostic tests or, occasionally, nucleic acid amplification tests such as polymerase chain reaction may be helpful in difficult cases (see also Chapters 6 and 21).

Typhoid and Paratyphoid Fever (Enteric Fevers)

Enteric fever is caused by *Salmonella enterica* serovar Typhi (*S. typhi*) or *Salmonella paratyphi*. Persistently rising fever, relative bradycardia, rose spots, and normal leukocyte counts with mild to moderate elevation of hepatic transaminases are all clues to the diagnosis; however, these characteristics are often absent. The organism can be cultured from the blood in >80% of patients during the first week of illness and from bone marrow aspirated from the iliac

crest in more than 90% of documented cases, if no antibiotics are administered before obtaining the culture. The organism can be cultured from stool during the incubation period occasionally, and in one-third to two-thirds of patients during the second through fourth weeks of illness.

Neither the oral nor the parenteral vaccine provides complete immunity (Chapter 5). In immunized populations, however, a higher percentage of individuals with enteric fever will have disease caused by *S. paratyphi*, although disease caused by *S. typhi* still occurs. Of the approximate 5700 cases of typhoid fever that occur annually in the United States, up to 75% are travel acquired. Of the 1902 laboratory-confirmed cases of typhoid fever reported by Lynch and colleagues (2009) between 1999 and 2006 in the United States where epidemiologic information was available, foreign travel in the preceding 30 days was reported by 79%, yet only 5% had received typhoid vaccine prior to travel. Seventy-three percent of cases were hospitalized, and 0.2% died. Resistance to antimicrobials has been reported for *S. typhi* isolates in many countries, although fluoroquinolones are usually effective against typhoid fever acquired outside the Indian sub-continent and Southeast Asia (Chapter 31).

Arboviral Diseases

Arboviral diseases are caused by arthropod-borne viruses; most are zoonoses (shared between humans and other vertebrate hosts). More than 400 arboviruses, classified into many families and genera, have been described (**Table 20.10**). Arboviral diseases are present throughout the tropics; however, some arboviruses, such as o'nyong-nyong, Mayaro, Ross River, Oropouche, and Rift Valley fever viruses, are limited in geographic distribution. Diagnosis usually depends on clinical suspicion and serologic confirmation, the latter generally requiring acute and convalescent serum samples.

The arboviral diseases can be divided into four syndromes based on clinical presentation: (1) undifferentiated fever, (2) dengue fever, (3) hemorrhagic fever, and (4) encephalitis. The syndrome of undifferentiated fever (e.g., Oropouche, Mayaro, and sand fly fever) is generally characterized by one or more of the following: fever, headache, myalgia, pharyngitis, coryza, nausea, vomiting, and diarrhea. The dengue fever syndrome (dengue, chikungunya, o'nyong-nyong, Sindbis, West Nile, Ross River viruses) is characterized by fever, rash, arthralgia, and leukopenia. The syndrome of hemorrhagic fevers (Lassa fever, Ebola, Marburg, Crimean-Congo, Argentine, Bolivian, dengue, yellow fever viruses) ranges from mild petechiae to severe purpura and bleeding diathesis. The 2014 West African outbreak of Ebola virus disease (EVD) underscores that prior estimates of the frequency of hemorrhagic manifestations in EVD are likely inflated. In this outbreak of EVD, which has led to >27,000 cases and >11,000 deaths, bleeding and hemorrhagic manifestations have been noted to occur in 5-15% of patients (Chertow et al. 2014; Qin et al. 2015).

Dengue Fever

Dengue is the most widespread arbovirus, distributed throughout the tropics, and frequently encountered in travelers returning from the tropics. Dengue virus is a single-stranded RNA flavivirus transmitted by the day-biting urban mosquito *Aedes aegypti* or the jungle mosquito *Aedes albopictus*. Four serotypes are recognized. Infection with one serotype results in immunity to that particular serotype; however, after a short period of cross-protection, individuals are susceptible to infection with another serotype.

Clinical infection ranges from a mild febrile syndrome to a severe dengue syndrome. Individuals with dengue who recover fully following defervescence are considered to have uncomplicated dengue, while those who deteriorate clinically are classified as having "warning signs," which include any of the following manifestations: abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, hepatic enlargement, and worsening thrombocytopenia in the setting of hemoconcentration. A minority of patients with warning signs will continue to deteriorate despite fluid resuscitation, and those are

TABLE 20.10 Epidemiology of Important Arboviruses[a]

Family (Genus) Virus	Human Disease	Distribution	Vector
Togaviridae (Alphavirus)			
Mayaro	Fever, arthritis, rash	South America	Mosquito
Ross River	Arthritis, rash, sometimes fever	Australia and South Pacific	Mosquito
Chikungunya	Fever, arthritis, hemorrhagic fever	The Americas, Africa, Asia, and Oceania	Mosquito
Eastern encephalitis	Fever, encephalitis	The Americas	Mosquito
Western encephalitis	Fever, encephalitis	The Americas	Mosquito
Venezuelan encephalitis	Fever, sometimes encephalitis	The Americas	Mosquito
Flaviviridae (Flavivirus)			
Dengue (four types)	Fever, rash, hemorrhagic fever	Worldwide (tropics)	Mosquito
Zika (Human disease)	Fever, rash, Guillan-Barre, microcephaly (during pregnancy) (Distribution)	The Americas (vector)	Mosquito
Yellow fever	Fever, hemorrhagic fever	Tropical Americas and Africa	Mosquito
St. Louis encephalitis	Encephalitis, hepatitis (rare)	The Americas	Mosquito
Japanese encephalitis	Encephalitis	Asia, Pacific	Mosquito
West Nile	Fever, rash, hepatitis, encephalitis	Asia, Europe, Africa, and North America	Mosquito
Kyasanur Forest	Hemorrhagic fever, meningoencephalitis	India	Tick
Omsk hemorrhagic fever	Hemorrhagic fever	Former Soviet Union	Tick
Tick-borne encephalitis	Encephalitis	Europe and Asia	Tick
Bunyaviridae (Bunyavirus)			
La Crosse encephalitis	Encephalitis	North America	Mosquito
Oropouche	Fever	Brazil and Panama	Midge
Bunyaviridae (Phlebovirus)			
Sand fly fever viruses	Fever	Asia, Africa, and tropical Americas	Sand fly, mosquito
Rift Valley fever	Fever, hemorrhagic fever, encephalitis, retinitis	Africa	Mosquito
Bunyaviridae (Nairovirus)			
Crimean-Congo hemorrhagic fever	Hemorrhagic fever	Asia, Europe, and Africa	Tick
Bunyaviridae (Hantavirus)			
Hantaan	Hemorrhagic fever, renal syndrome	Asia	Rodent-borne
Puumala	Hemorrhagic fever, renal syndrome	Europe	Rodent-borne
Sin Nombre	Hantavirus pulmonary syndrome	Western USA	Rodent-borne
Arenaviridae (Arenavirus)			
Junin	Hemorrhagic fever	Argentina	Rodent-borne
Machupo	Hemorrhagic fever	Bolivia	Rodent-borne
Lassa fever	Hemorrhagic fever	West Africa	Rodent-borne

TABLE 20.10 Epidemiology of Important Arboviruses—cont'd

Family (Genus) Virus	Human Disease	Distribution	Vector
Reoviridae (Orbivirus)			
Colorado tick fever	Fever	Western USA	Tick
Filoviridae (Filovirus)			
Marburg	Hemorrhagic fever	Africa	Unknown
Ebola	Hemorrhagic fever	Africa	Unknown

Adapted from: Shope, R.E., 1992. In: Wyngaarden, J.B., Smith, L.H., Bennett, J.C. (Eds.), Cecil's Textbook of Medicine, nineteenth ed. Saunders, Philadelphia.
[a]Some of the viruses listed are not transmitted by arthropods and thus are not arboviruses.

considered to have severe dengue, characterized by severe plasma leakage, severe bleeding, or organ failure (WHO 2009).

The incubation period of dengue is 5-8 days. A viral prodrome of nausea and vomiting is common, followed by high fever for a mean of 5 days; the fever often lyses abruptly. Myalgia and arthralgia are particularly prominent, giving rise to the common name of "breakbone fever." Headache (especially retro-orbital), lymphadenopathy (frequently cervical), and/or rash (scarlatiniform, maculopapular, or petechial; characteristic "islands of white macules on a sea of red") frequently develop. The rash may occur late during the course of illness, and fever may reappear after several days. (*Note*: this "saddleback" fever pattern is present in about 60% of cases.)

Previous infection with one serotype of virus may predispose an individual to more severe disease on infection with another serotype. This immune enhancement of viral pathogenesis is thought to result from immunoglobulin-mediated dengue virus uptake into macrophages, where growth is favored. Thus the hemorrhagic fever/shock syndrome, which is most common in indigenous children, is unlikely to occur in a traveler who has not been previously infected with dengue. Prolonged convalescent periods, characterized by extreme fatigue often persisting for months, have been noted by many travelers who have acquired dengue fever. Dengue vaccine trials in endemic areas show some benefit in children.

Chikungunya

Chikungunya virus infection has been historically noted among travelers from Southeast Asia and Africa. However, in late 2013, the virus emerged for the first time in the Americas, leading to a widespread and ongoing outbreak in the Caribbean and Central and South America affecting at least 44 individual countries, with cases numbering into the hundreds of thousands. This has resulted in high numbers of cases among North American and European travelers to the Caribbean and Central America, in particular. This disease presents in a fashion similar to dengue fever, although incubation and duration of symptoms are typically more prolonged. Myalgia and arthralgia are particularly severe with chikungunya, with function-limiting arthropathy persisting for years in a minority of patients.

Zika

Zika virus was discovered in Uganda in 1947, and human infectinos were extraordinarily rare until 2015, when an epidemic began to sweep across South and Central America. Most adult patients have a clinical illness very similar to Dengue and Chikungunya, although neurological injury such as Guillan-Barre has been described. Of greatest concern is its association with microcephaly if the patient is pregnant during infection. Women who return from endemic areas with fever should be assessed for this infection, and if infected and pregnant, counseled on strategies for aggressive fetal monitoring or termination options.

Yellow Fever

In the Americas, yellow fever is transmitted by *Haemagogus* mosquitoes in the jungle environment and *A. aegypti* in urban settings. In Africa, transmission to humans occurs via *Aedes* spp. Historically, in both urban and rural environments, only 50-200 cases of yellow fever per year have been reported from the tropical Americas. However, yellow fever is an emerging problem in the Amazon and other jungle regions of Brazil, Colombia, Venezuela, and Peru, with resurgence of the disease in the early 2000s leading to mass vaccination initiatives. Sporadic urban transmission still occurs in large outbreaks in Africa. Although *A. aegypti* is ubiquitous in the Far East, yellow fever virus transmission has never been reported from this region. The reason is unclear, but either the lack of virus importation into the region or possible immune cross-resistance induced by endemic dengue immunity may be responsible. The spectrum of clinical disease ranges from a dengue fever-like illness to a severe hemorrhagic illness associated with hepatic and renal failure. The disease is almost 100% preventable by vaccination with live attenuated 17D-strain vaccine (Chapter 5). Among unvaccinated travelers from the United States and Europe, nine cases of yellow fever occurred between 1970 and 2011, five of which were acquired in sub-Saharan Africa, and four in South America. Eight of these cases were fatal.

Hemorrhagic Syndromes

Viruses causing hemorrhagic syndromes, such as Lassa fever virus, Ebola virus, Marburg virus, and Machupo virus, have been associated with life-threatening infections that can be spread nosocomially. Patients who are suspected of having one of these viruses should be placed in airborne and contact isolation. Laboratory work should be kept to a necessary minimum and the laboratory alerted to the possibility of contagious virus in patient specimens. The CDC and state health department should be contacted immediately.

An arthropod vector has not been identified for many of these viruses, such as Lassa fever, which is transmitted via contact with rodent reservoirs in rural West Africa or with infected humans. Early symptoms include fever, malaise, weakness, and myalgia. A few days later, cough, pharyngitis, and chest and epigastric pain develop. Vomiting and diarrhea occur by about day 5, associated with fever of 39-40° C. By the sixth day, respiratory distress, cardiac instability, hepatic and renal failure, and hemorrhagic phenomena begin to appear. Lassa fever can be diagnosed by either the isolation of virus or the demonstration of a fourfold increase in antibody titer. Early treatment with ribavirin may improve outcome with Lassa fever virus, Hantaan virus, and other hemorrhagic viruses with the exception of Ebola, yellow fever, and dengue viruses. Other viruses of importance are listed in **Table 20.11**. (See also Chapter 28.)

Rickettsial Diseases

Rickettsial diseases are acute, usually self-limited febrile illnesses caused by obligate intracellular Gram-negative bacteria of the order Rickettsiales. Rickettsiae can be divided into the spotted fever group and the typhus fever group. All are transmitted by ticks, fleas, lice, or mites. Rickettsiae are widely distributed throughout the world (**Table 20.12**).

The spectrum of illness ranges widely and includes subclinical infection. Incubation periods for the various diseases vary widely, on the order of 2-30 days (**Table 20.13**). Clinical illness is generally characterized by an abrupt onset of fever, chills, and sweats, frequently associated with rash, headache, conjunctivitis, pharyngitis, epistaxis, myalgias, arthralgias, and hepatosplenomegaly. An eschar often develops at the site of the bite of the mite or tick in scrub typhus, due to *Orientia tsutsugamushi*, and the spotted fever group rickettsioses. Vasculitis underlies the typical pathologic manifestations of rickettsial disease. Complications are rare but include encephalitis, renal failure, and shock.

Most rickettsial disease reported in the United States is acquired domestically (e.g., Rocky Mountain spotted fever). Spotted fever group rickettsioses, including Mediterranean spotted fever/boutonneuse fever and African tick bite fever, appear to be the most common

Continued text to page 293

TABLE 20.11 Epidemiology and Clinical Characteristics of Viral Hemorrhagic Fevers

Disease	Clinical Syndrome	Geographic Distribution	Vector
Yellow fever	Ranges from mild febrile illnesses to severe hepatitis and renal failure (with albuminuria); biphasic course of illness may be noted	Tropical South America and sub-Saharan Africa	*Aedes aegypti* mosquito *Haemagogus* mosquito (urban Americas)
Dengue	Classic dengue: fever, severe myalgia/arthralgia, and morbilliform rash Dengue hemorrhagic fever: shock and DIC	Tropical and subtropical regions of the Americas, Africa, Asia, and Australia	*Aedes aegypti* mosquito
Lassa fever	Fever, severe headache, lumbar pain, chest pain, and thrombocytopenia; possible encephalitis, pneumonitis, and myocarditis	Sub-Saharan Africa	None (high potential for person-to-person transmission)
Argentine hemorrhagic fever (Junin virus)	Insidious onset of fever, myalgia, headache, conjunctivitis, epigastric pain, nausea, and vomiting; possible shock	Argentina (especially Buenos Aires province)	None
Bolivian hemorrhagic fever (Machupo virus)	Similar to Argentine hemorrhagic fever	Bolivia (Department of Beni)	None
Marburg virus	Abrupt onset of fever, headache, conjunctivitis, myalgia, nausea, and vomiting; severe hemorrhagic complications and shock are common	Laboratory outbreaks involved with handling infected monkey tissues/cells	None (high potential for person-to-person transmission)
Ebola virus	Similar to Marburg virus; in West African outbreak, hemorrhagic complications are uncommon; large volume diarrhea common	Large outbreak in West Africa beginning in early 2014; isolated outbreaks in rural sub-Saharan Africa	None (high potential for person-to-person transmission)
Crimean-Congo hemorrhagic fever	Abrupt onset of fever, headache, arthralgia, myalgia, conjunctivitis, and abdominal pain; purpura and ecchymoses are common	Africa, Middle East, and Eastern Europe	*Hyalomma* species (ticks) (potential for nosocomial transmission)
Hemorrhagic fever with renal syndrome (hantavirus)	Abrupt onset of fever, headache, lethargy, abdominal pain associated with oliguria and acute renal failure; petechiae are common	Balkans, former Soviet Union, Korea, and China	None

DIC, Disseminated intravascular coagulopathy.

TABLE 20.12 Epidemiology of Rickettsial Diseases

Disease	Organism	Natural Cycle		Usual Mode of Transmission to Humans	Common Occupational or Environmental Association	Geographic Distribution
Typhus Group						
Murine typhus	*Rickettsia mooseri* (*Rickettsia typhi*)	Fleas	Rodents	Infected flea feces into broken skin or aerosol to mucous membrane	Rat-infected premises (shops, warehouses)	Scattered foci (worldwide grain elevators)
Epidemic typhus	*Rickettsia prowazekii*	Body lice	Humans	Infected feces or crushed lice into broken skin, or aerosol to mucous membranes	Lice-infected human population with louse transfer	Worldwide
Brill-Zinsser disease	*R. prowazekii*	Recrudescence months to years after primary attack of louse-borne typhus			Unknown, stress	Worldwide
Spotted Fever Group (Selected Examples)						
Rocky Mountain spotted fever	*R. rickettsii*	Ixodid ticks	Ticks/small mammals	Tick bite, mechanical transfer to mucous membranes, ?air-borne	Tick-infested terrain, houses, dogs	Western hemisphere
Ehrlichiosis	*Ehrlichia canis*	Ticks	Dogs	Tick bite	Tick-infested areas	At least 12 states in USA, primarily southern states
African tick bite Fever	*Rickettsia africae*	*Amblyomma* ticks	Ticks	Tick bite	Game hunting; safari	Southern Africa
Boutonneuse fever	*Rickettsia conorii*	Ixodid ticks	Ticks/rodents, dogs	Tick bite	Tick-infested terrain, houses, dogs	Mediterranean littoral, Africa, and Indian subcontinent
Rickettsialpox	*Rickettsia akari*	Mouse mites	Mites/mice	Mouse mite bite	Unique mouse- and mite-infested premises (incinerators)	USA, former Soviet Union, Korea, and Central Africa

Others						
Q fever	*Coxiella burnetii*	Ticks	Ticks/mammals	Inhalation of dried air-borne infective material; tick bite	Domestic animals or products, dairies, lambing pens, slaughterhouses	Worldwide
Scrub typhus (tsutsugamushi disease)	*Orientia tsutsugamushi* (multiple serotypes)	Chiggers (harvest mites)	Chiggers/ rodents	Chigger bite	Chigger-infested terrain; secondary scrub, grass airfields, golf courses	Asia, Australia, New Guinea, and Pacific Islands
Trench fever	*Bartonella quintana*	Body lice	Humans	Infected feces or crushed louse into broken skin; aerosol to mucous membranes	Lousy human population with louse transfer	Africa, Mexico, South America, and Eastern Europe

Adapted from: Hornick, R.B., 1992. In: Wyngaarden, J.B., Smith, L.H., Bennett, J.C. (Eds.), Cecil Textbook of Medicine, nineteenth ed. Saunders, Philadelphia.

TABLE 20.13 Clinical Features of Important Rickettsial Diseases

Disease	RASH							
	Usual Incubation Period in Days (Range)	Eschar	Onset, Day of Disease	Distribution	Type	Usual Duration of Disease in Days[a] (Range)	Usual Severity[b]	Fever after Chemotherapy (h)
Typhus Group								
Murine typhus	12 (8-16)	None	5-7	Trunk → extremities	Macular, maculopapular	12 (8-16)	Moderate	48-72
Epidemic typhus	12 (10-14)	None	5-7	Trunk → extremities	Macular, maculopapular, petechial	14 (10-18)	Severe	48-72
Brill-Zinsser disease	–	None		Trunk → extremities	Macular	7-11	Relatively mild	48-72
Spotted Fever Group (Selected Examples)								
Rocky Mountain spotted fever	7 (3-12)	None	3-5	Extremities → trunk, face	Macular, maculopapular, petechial	16 (10-20)	Severe	72
Ehrlichiosis	7-21	None	Rare?	Unknown	Petechial	7 (3-19)	Mild	72
Boutonneuse fever	5-7	Often present	3-4	Trunk, extremities, face, palms, soles	Macular, maculopapular, petechial	10 (7-14)	Moderate	–
Rickettsialpox	?9-17	Often present	1-3	Trunk → face, extremities	Papulovesicular	7 (3-11)	Relatively mild	–
Others								
Q fever	10-19	None		None		(2-21)	Relatively mild[c]	48 (sometimes slow)
Scrub typhus (tsutsugamushi disease)	1-12 (9-18)	Often present	4-6	Trunk → extremities	Macular, maculopapular	14 (10-20)	Mild to severe	24-36

Adapted from Hornick, R.B., 1992. In: Wyngaarden, J.B., Smith, L.H., Bennett, J.C. (Eds.), Cecil Textbook of Medicine, nineteenth ed. Saunders, Philadelphia.
[a]Untreated disease.
[b]Severity can vary greatly.
[c]Occasionally, subacute infections occur (e.g., hepatitis, endocarditis)

rickettsial diseases of travelers, accounting for 231 of 280 cases of rickettsial disease among travelers reported by GeoSentinel between 1996 and 2008 (Jensenius et al. 2009). Typhus fever group rickettsioses are endemic to areas in southern Europe, Africa, and the Middle East, although most cases are also reported in travelers to Africa.

Diagnosis requires clinical suspicion (often mandating empiric antibiotic therapy) and specific serologies. Therapy consists of doxycycline (200 mg/day in divided doses) generally for 3-4 days after defervescence and a minimum of 1 week total therapy. Recent evidence suggests that short courses of macrolide antibiotics, such as azithromycin or clarithromycin, may be acceptable alternatives for the therapy of rickettsioses other than Rocky Mountain spotted fever.

Helminths

Schistosomiasis (Bilharziasis)

Schistosomiasis is caused by a fluke and transmitted by freshwater exposure in endemic regions. Katayama fever, or acute schistosomiasis, develops 2-10 weeks after exposure. This serum sickness-like illness is believed to represent a reaction against antigen–antibody complexes formed as a result of egg deposition. This syndrome is most severe in *Schistosoma japonicum* infections, in which egg production is greatest. Characteristic clinical manifestations include fevers, chills, sweating, headache, cough, lymphadenopathy, hepatosplenomegaly, and eosinophilia. Although death has been reported in *S. japonicum* infections, most patients with Katayama fever experience a self-limited illness that is commonly undiagnosed. Travelers appear to be more likely to develop this syndrome than those raised in endemic areas. Serologic studies are helpful in the diagnosis. Recommended treatment involves administration of praziquantel and corticosteroids (see Chapter 48). Mounting evidence suggests that asymptomatic travelers returning from high-risk areas should be screened (serologically and/or with stool/urine ova and parasites, the latter >6 weeks after exposure) and treated.

Filariasis

The filariasis syndromes associated with fever include onchocerciasis (river blindness), lymphatic filariasis (lymphangitis, often complicated by bacterial superinfection), loiasis, and nocturnal fever with or without pulmonary symptoms resulting from circulating microfilariae. Of these entities, loiasis is most commonly seen in travelers and short-term residents of risk areas (rainforest regions of Central Africa). Eosinophilia is common in patients with filariasis. The diagnosis is usually established by the demonstration of microfilariae in skin snips (onchocerciasis) or in blood. (*Note*: in lymphatic filariasis, the microfilariae circulate nocturnally, while microfilaremia of *Loa loa* peaks in the late afternoon.) Serologic study may be helpful when the disease is suspected (see Chapter 47).

Strongyloidiasis

Strongyloidiasis, usually acquired when larvae in contaminated soil penetrate the skin, rarely causes a febrile illness in travelers. However, a Löffler syndrome, characterized by pulmonary infiltrates with eosinophilia, may occur during the obligate lung migration phase of larvae and may be accompanied by fever. Immunocompromised hosts, particularly due to HTLV-1 or corticosteroids, can develop a life-threatening hyperinfection syndrome, which is frequently complicated by significant disseminated strongyloidiasis outside the gastrointestinal tract (see Chapter 45).

Trichinosis

Trichinosis, usually associated with high-grade eosinophilia, muscle pain, and fever, can be acquired by travelers who ingest undercooked meat (see Chapter 49).

Paragonimiasis

Paragonimiasis is an illness caused by a lung fluke that induces a febrile response either during its migration to the lungs or by its obstruction or destruction of lung parenchyma. Hemoptysis can occur, mimicking pulmonary tuberculosis. The disease is usually acquired

by ingestion of raw freshwater crustaceans in Asia, South America, and Africa, though case series are reported in the United States from imported freshwater crab or local crawfish ingestion. Diagnosis can be established by examination of the sputum and stool for ova. Serologic studies are available (see Chapter 48).

Echinococcosis

The ingestion of food or water contaminated by echinococcal eggs from canid feces can cause hydatid cyst disease involving the lungs or liver. Fever is usually absent unless the cyst or cysts become secondarily infected or rupture (see Chapter 46).

Protozoa

Amebiasis

E. histolytica is usually acquired by ingesting cysts in water or food contaminated by human feces but may be transmitted sexually. Both amebic dysentery and amebic liver abscess may cause fever. Amebic liver abscess is associated with right upper quadrant discomfort, hepatomegaly, an elevated right hemidiaphragm, and high serologic reactivity to *E. histolytica* antigens. Often, *E. histolytica* cannot be identified in the stool at the time of presentation of amebic abscess. Treatment is with metronidazole plus another agent to clear luminal cysts, such as iodoquinol (see Chapter 32).

Chagas Disease

Chagas disease (American trypanosomiasis), caused by infection with *Trypanosoma cruzi*, is typically acquired by dwelling in mud or thatched-roof housing, via the feces of the reduviid bug, which defecates on the patient during a silent blood meal. In addition, transmission in Latin America is often congenital or via blood transfusion in endemic countries and occasionally in the United States. It is increasingly recognized as a food-borne illness when cane-sweetened juices are contaminated by crushed reduviid bugs. In typical transmission, after an incubation period of 1-2 weeks, *T. cruzi* causes a febrile illness during the acute stage of infection that persists for 2-4 weeks. The illness is accompanied by local swelling at the site of inoculation of trypanosomes (Romaña sign), lymphadenopathy, hepatosplenomegaly, and influenza-like symptoms. Trypanosomes may be seen during the acute stage of infection in peripheral blood by blood smear or in biopsy specimens obtained from the site of inoculation. Serology studies may be helpful. Treatment during the acute stage of infection with benznidazole or nifurtimox is beneficial in attenuating the progression to chronic Chagas disease. This disease is rare among travelers but is increasingly recognized in nonendemic countries among Latin American immigrants (see Chapter 26).

African Trypanosomiasis

African trypanosomiasis (infection with *Trypanosoma brucei gambiense* or *T. brucei rhodesiense*) cause febrile syndromes due to circulating trypanosomes. West African disease often presents in a subacute or chronic fashion, whereas East African disease is less well adapted to humans and thus has a more fulminant course. Both diseases are transmitted by the bite of the tsetse fly in Africa. Occasionally, a chancre can be seen at the site of inoculation during acute infection. Lymphadenopathy is common, particularly in the posterior cervical chain. Later, the trypanosomes invade the central nervous system, and lumbar puncture must be performed to determine which treatment regimen should be administered. If disease has progressed to the central nervous system, treatment with arsenicals, such as melarsoprol, or difluoromethylornithine is recommended for East and West African trypanosomiasis, respectively. African trypanosomiasis is uncommon among travelers, although clusters have been reported, mainly in travelers returning from East Africa. Both East and West African disease are ultimately fatal without treatment, so recognition and rapid action is essential (see Chapter 27).

Visceral Leishmaniasis

Visceral leishmaniasis, or kala-azar, is characterized by hepatosplenomegaly, severe wasting, and fevers, a syndrome evocative of lymphoma. *Leishmania* spp. are transmitted by the bite

of the sand fly. The kala-azar syndrome is usually caused by *Leishmania donovani*. Visceral leishmaniasis is extremely uncommon among travelers. Treatment is with amphotericin B in lipid formulations, pentavalent antimonials, or miltefosine (see Chapter 39).

Toxoplasmosis

Toxoplasmosis, which can cause an acute febrile syndrome, may be acquired by travelers via the consumption of undercooked meat. Transmission may occur in unexpected places, such as France, where infection with *Toxoplasma gondii* is much more common because of the popular ingestion of uncooked meat.

Bacteria

Tuberculosis

Tuberculosis is an uncommon disease among short-term travelers (**Table 20.1**). Travelers at increased risk are those going abroad to perform medical service and those residing abroad for prolonged lengths of time. Occasionally, tuberculosis transmission has been reported among air travelers as the result of relatively poor air turnover on airlines and the presence of a passenger with active pulmonary tuberculosis. In a study of American healthcare workers returning from Botswana, tuberculin skin test conversion occurred in 4.2%, corresponding to a rate of 6.87 per 1000 person-weeks of travel (Szep et al. 2014). Healthcare workers, missionaries, teachers, and others who anticipate close daily contact with resident populations in countries where the incidence of tuberculosis is high should receive the tuberculin skin test before travel to establish a baseline status, and 8-12 weeks following travel (see Chapter 25).

Meningococcal Meningitis

Meningococcal infection occurs sporadically in travelers to endemic areas (sub-Saharan Africa and Nepal) and in epidemics during times of crowding. An example of the latter is the reported high incidence of meningococcal disease and carriage after pilgrimage to Mecca. Purpuric lesions and signs of meningismus are helpful diagnostic clues, but individuals may present with only fever and respiratory symptoms. Diagnosis is established by culture of blood and cerebrospinal fluid, and treatment with parenteral ceftriaxone is usually effective. Close contacts of documented cases should receive prophylaxis with rifampin or ciprofloxacin. Travelers going to areas of known meningococcal transmission should undergo meningococcal vaccination before departure (see Chapter 5).

Leptospirosis

Leptospirosis is acquired by contact with water contaminated by animal urine containing spirochetes. It is common in the tropics and subtropics (Chapter 23). This disease may be contracted by abattoir workers, swimmers, and campers. Large outbreaks have occurred among triathletes in Illinois (98 cases) and competitive swimmers in Borneo (70 cases). Clinical illness ranges from relatively mild disease to fulminant hepatic failure with icterohemorrhagic fever (Weil's disease). Definitive diagnosis is based on either serologic studies or the demonstration of leptospires in specimens of clinical fluids. As with rickettsioses, empiric treatment is often considered.

Brucellosis

Brucellosis is usually transmitted by unpasteurized dairy products but may be encountered in abattoirs. Illness ranges from an indolent febrile syndrome to fulminant endocarditis. Brucellosis is occasionally encountered in the post-travel setting, although laboratory acquisition is well documented and remains a risk for medical and laboratory workers who volunteer or work overseas. In their study of >42,000 ill returned travelers entered into the GeoSentinel database between 2007 and 2011, Leder and colleagues (2013) reported 33 cases of acute brucellosis, most of which were acquired in India, the Sudan, and Iraq.

Plague

Plague is reported to be epidemic in humans in certain regions of Vietnam and is endemic in rodent populations in the southwestern United States and other areas of the world. Larger outbreaks can occur, as in India in 1994. Plague causes a clinical syndrome of painful regional lymphadenitis associated with necrotizing pneumonia and septicemia. Prophylactic doxycycline may be given to travelers at risk, since the plague vaccine is not widely available (see Chapter 5).

Melioidosis

Melioidosis, caused by the Gram-negative bacterium *Burkholderia pseudomallei*, produces a tuberculosis-like illness or septicemia. The disease is particularly prevalent in Southeast Asia, where it is especially common in rice-paddy workers. Many Vietnam veterans have serologic evidence of past infection with *B. pseudomallei*. Like tuberculosis, the bacteria may remain dormant for many years before reactivating and causing illness.

Relapsing Fever

Relapsing fever (caused by *Borrelia* species) is a worldwide tick-borne endemic disease, but louse-borne human–human transmission still occurs in highlands of Ethiopia, Sudan, Somalia, Chad, Bolivia, and Peru. Diagnosis depends on the demonstration of extracellular spirochetes by blood smear and Giemsa staining.

Bartonellosis (Oroya Fever)

Bartonellosis, caused by *Bartonella bacilliformis*, is transmitted by sand flies only in Andean river valleys with elevations between 2000 and 8000 ft in Peru, Ecuador, and Colombia. This infection can lead to acute hemolysis (i.e., Oroya fever), in which intraerythrocytic organisms may be detected on pathologic stains (e.g., Giemsa) or in chronic, angioproliferative skin lesions (i.e., verruga peruana, lesions that may be sessile, miliary, nodular, pedunculated, or confluent and may be as large as 1-2 cm). A newly described species, *Bartonella rochalimae*, was reported to cause an Oroya fever-like illness, characterized by anemia, fever, and splenomegaly, in an American traveler to Peru (Eremeeva et al. 2007). The patient had been traveling in an area endemic for *B. bacilliformis*, but to date, no clear vector has been identified. This case highlights the sustained possibility of discovering novel pathogens as international travel becomes increasingly attractive and affordable.

Anthrax

Cutaneous anthrax generally has been associated with exposure to infected animals, contaminated animal hides, and wool. Because *Bacillus anthracis* spores can survive for prolonged periods, contaminated hides or wool remain infectious and may rarely be responsible for disease transmission. Anthrax is sometimes associated with a local eschar, where bacteria proliferate and invade the bloodstream. Travelers purchasing souvenirs or articles of clothing made with contaminated animal hides or wool are a group at theoretical risk for the acquisition of anthrax; hunters are another potential group at risk. In contrast, inhalational anthrax is usually thought to be associated with bioterrorism.

Sexually Transmitted Infections

Gonorrhea, syphilis, chlamydia, lymphogranuloma venereum, herpes simplex virus, HIV, granuloma inguinale, and chancroid are all sexually transmitted diseases that may give rise to fevers (see Chapters 41-44).

Viruses

Respiratory and Enteric Viruses

Common respiratory and enteric viruses are the most common causes of fever in travelers, accounting for over 50% of cases of febrile illness in travelers in most case series.

Hepatitis

Hepatitis viruses are a relatively common cause of fever in travelers (100-200/100,000 travelers); prodromal symptoms associated with fever may precede icterus. Hepatitis A occurs most frequently, but >90% of cases could be prevented by pre-travel immunization with hepatitis A vaccine. Adults over the age of 40 years who acquire hepatitis A are at much greater risk of having a complicated course or dying of their disease than are those who are younger. Hepatitis B and C may occur in healthcare workers, individuals with a history of sexual contact abroad, and patients who receive blood transfusions, although the hepatitis B immunization is also highly effective (see Chapter 22). Hepatitis E has been serologically confirmed in many returned travelers; it undoubtedly occurs more often. In long-term travelers to the developing world, the seroconversion rate for hepatitis E is ~5%.

Human Immunodeficiency Virus (HIV)

Acute HIV infection, resulting from sexual activity, blood transfusion, and intravenous drug use, has been reported among returned travelers (see Chapter 41). In their analysis of GeoSentinel data, Leder and colleagues (2013) reported 84 cases of acute HIV among >42,000 ill returned travelers, making HIV the seventh most common specific cause of fever in this group. Rash and lymphadenopathy combined with appropriate history can be clues to suspect primary infection. Plasma RNA levels are more sensitive than serodiagnostic tests, which may be negative in the early period of infection.

Infectious Mononucleosis

Acute infection with Epstein-Barr virus (EBV) may occur in susceptible travelers, especially in the 15- to 30-year-old age group. Hepatosplenomegaly, lymphadenopathy, mucopurulent pharyngitis, heterophile antibodies, and the presence of atypical lymphocytes on the blood smear are helpful clues. Specific EBV serologies are useful to establish the diagnosis of acute infection. Cytomegalovirus (CMV) infections may cause an infectious mononucleosis-like illness with elevated hepatic transaminases in travelers and may be diagnosed by CMV serologies.

Measles

Rubeola (measles) remains an important cause of morbidity and mortality in developing countries and poses a substantial risk to travelers who have not received adequate immunization. Furthermore, the syndrome of atypical measles may result from exposure to wild virus in individuals who may have received killed virus vaccine (used in the United States before 1963). A large outbreak involving a US theme park in 2014 underscored the risk of measles to unvaccinated individuals and the risk of exported disease via commercial air travel. Complications of measles include progressive pneumonitis (especially in pregnant or immunocompromised patients), pulmonary bacterial superinfection, and encephalitis.

Fungi

Endemic mycoses such as histoplasmosis and coccidioidomycosis are becoming increasingly recognized among international travelers and can present as undifferentiated fever. Among 13 cases of acute pulmonary histoplasmosis in a group of US travelers to Martinique, trekking through a mountain tunnel full of bats emerged as the common epidemiologic risk factor. Participation in construction projects at an orphanage in Tecate, Mexico was similarly associated with a cluster of cases of coccidioidomycosis among US travelers. Penicilliosis can also be acquired by travelers. Endemic mycoses can present as a systemic febrile or flu-like illness, with or without accompanying respiratory, cutaneous, or articular manifestations, and should therefore be considered in the differential diagnosis of post-travel fever.

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